IJPSR (2023), Volume 14, Issue 9 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 December 2022; received in revised form, 20 March 2023; accepted 30 May 2023; published 01 September 2023

PATHOPHYSIOLOGY OF ASTHMA: A REVIEW

P. N. Bhong [*1], P. J. Patil [1] and P. K. Ghadage [2]

Marathwada Mitramandals College of Pharmacy [1], Thergaon, Pune - 411033, Maharashtra, India.
JSPM's Rajarshi Shahu College of Pharmacy and Research [2], Tathawade, Pune - 411033, Maharashtra, India.

Keywords:

Asthma, Airway hyper-responsiveness, Acute bronchoconstriction, Airway remodeling, Mediators of asthma

Correspondence to Author:
Prabha N. Bhong

Assistant Professor,
Marathwada Mitramandals College of Pharmacy, Thergaon, Pune - 411033, Maharashtra, India.

E-mail: prabha.1may@gmail.com

ABSTRACT: This review aims to provide a brief overview of different mechanisms involved in the pathophysiology of asthma, a variety of cells, and mediators released from these cells, which have an important role in the pathophysiology of asthma. Asthma is a heterogeneous disease which having complex pathophysiology and affects many individuals. Asthma is an inflammatory disease in the airway, leading to airway hyperresponsiveness, obstruction, mucus hyper-production, and airway wall remodeling. Status asthmatics is characterized by hypoxemia, hypercarbia, and secondary respiratory failure. The structural, mechanical, and inflammatory abnormalities related to asthma and the different mediators like histamine, cytokines, leukotrienes, thromboxane's inflammatory cells eosinophils, mast cells are important in asthma pathophysiology. TGF-h and IL-11 are the main cytokines that are involved in airway remodeling. Mast cells are responsible for initiating inflammatory responses after exposure to allergens and the resulting immediate bronchoconstriction. Macrophages releasing the mediators may be responsible for amplifying the inflammatory process. Dendritic cells act as antigen-presenting cells and play a role in the chemotaxis of T cells. Eosinophils are a source of lipid-derived mediators (leukotrienes), and eosinophil granules contain major basic protein (MBP), eosinophil cationic factor (ECF), eosinophil-derived neurotoxin and eosinophil-peroxidase. These may be responsible for respiratory tract fibrinogenesis and airway hyperresponsiveness. Adenosine causes bronchoconstriction in asthmatics but not in non-asthmatics. Toll-like receptors serve as receptors for products generated by pathogens. The etiology of asthma is increasingly associated with interactions between genetic susceptibility, host factors, and environmental exposures.

INTRODUCTION: Asthma is a chronic inflammatory disease of the airways characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli. It is manifested physiologically by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy and clinically by paroxysms of dysponea, cough, and wheezing. As asthma is an episodic disease, with acute exacerbations interspersed with symptom-free periods. Typically, most attacks are short-lived, lasting minutes to hours and clinically the patient seems to recover completely after an attack.

However, there can be a phase in which the patient experiences some degree of airway obstruction daily. This phase can be mild, with or without severe superimposed episodes, or much more serious, with severe obstruction persisting for days or weeks; the latter condition is known as status asthmatics. In unusual circumstances, acute episodes can cause death [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(9).4373-83

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(9).4373-83

Asthma is a disease characterized by reversible airway obstruction, bronchial hyper-responsiveness, inflammation [2]. epithelial cell sloughing, and lung remodeling [3].

Classification of Asthma [4]: Based on the stimuli initiating bronchial asthma, two broad etiologic types are traditionally described: extrinsic (allergic, atopic) and intrinsic pattern. Contrasting features of the two major types of asthma.

TABLE 1: TYPES OF ASTHMA

Feature	Extrinsic Asthma	Intrinsic Asthma
Age at onset	In childhood	In adult
Personal/family history	Commonly present	Absent
Preceding allergic illness (atopy)	Present (e.g. rhinitis, urticaria, eczema)	Absent
Allergens	Present (dust, pollens, dandersetc.)	None
Drug hypersensitivity	None	Present (usually to aspirin)
Serum IgE level	Elevated	Normal
Associated chronic bronchitis, nasal polyps	Absent	Present
Emphysema	Unusual	Common

Extrinsic (Atopic, Allergic) Asthma: Hypersensitivity to various extrinsic antigenic substances or 'allergens' is usually present in these cases. Most of these allergens cause ill effects by inhalation *e.g.* house dust, pollens, animal danders, moulds *etc*. Occupational asthma stimulated by fumes, gases and organic and chemical dusts is a variant of extrinsic asthma. There is increased level of IgE in the serum and positive skin test with the specific off ending inhaled antigen representing an IgE-mediated type I hypersensitivity reaction which includes an 'acute immediate response' and a 'late phase reaction

Acute immediate response is initiated by IgE-sensitised mast cells on the mucosal surface. Mast cells on degranulation release mediators like histamine, leukotrienes, prostaglandins, platelet activating factor and chemotactic factors for eosinophils and neutrophils. The net effects of these mediators are bronchoconstriction, oedema, mucus hyper secretion and accumulation of eosinophils and neutrophils.

The late-phase reaction follows the immediate acute response and is responsible for the prolonged manifestations of asthma. It is caused by excessive mobilization of blood leucocytes, including basophils, eosinophils, and neutrophils. These result in the further release of mediators, accentuating the effects mentioned above. In addition, inflammatory injury is caused by neutrophils and by the major basic protein (MBP) of eosinophils.

Intrinsic (Idiosyncratic, Non-atopic) Asthma: This type of asthma develops later in adult life with a negative personal or family history of allergy, negative skin test and normal serum levels of IgE. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic) [5]. There are no recognisable allergens but about 10% of patients become hypersensitive to drugs, most notably to small doses of aspirin (aspirin-sensitive asthma). Intrinsic asthma may be due to an imbalance between parasympathetic and sympathetic airway response. The release of Acetylcholine by the parasympathetic nervous system causes bronchoconstriction, the sympathetic nervous system by stimulating adenyl-cyclase cause bronchodilatation [5].

Some other types of asthma are

Adult-onsetasthma: Some adults, particularly women, present with asthma for the first time in adult life. These patients tend to be non-allergic, and often require higher doses of ICS or are relatively refractory to corticosteroid treatment. Occupational asthma (i.e. asthma due to exposures at work) should be ruled out in patients presenting with adult-onset asthma.

Asthma with Persistent Airflow Limitation: some patients with long-standing asthma develop airflow limitation that is persistent or incompletely reversible. This is thought to be due to airway wall remodeling.

Asthma with Obesity: some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation [5].

Exercise –Induced Asthma: (or Cold-dry-air-Induced) [6, 7]: It is caused by an acute large increase

in the air entering the airways that require heating and humidifying. In susceptible individuals, this results in inflammatory, neuronal, and vascular changes, ultimately resulting in bronchial smooth muscle contraction and symptoms of dyspnea, cough, chest tightness, mucus production, and wheezing.

During exercise, catecholamine release initiates a bronchodilatory response in both healthy subjects and asthmatic patients. The results include progressive bronchoconstriction, with maximal obstruction occurring 5 to 10 minutes after the cessation of exercise and the remission of pulmonary function parameters within 30 to 60 minutes. Exercise-induced asthma more often appears after short periods (5 to 10 minutes) of intense exercise and may also occur after 30 minutes of continuous exercise. Patients may exercise through their symptoms, with the gradual spontaneous resolution of bronchoconstriction. The pathogenesis of exercise-induced asthma is associated with three major factors: minute ventilation tidal volume times the respiratory rate per minute, the inspired air's temperature and humidity and the patient's baseline airway reactivity. High levels of VE are required for more strenuous work and are associated with a greater degree of airway obstruction [6, 8].

Status Asthmaticus: A medical emergency, an extreme asthma exacerbation characterized by hypoxemia, hypercarbia, and secondary respiratory failure. All patients with bronchial asthma are at risk of developing an acute episode with a progressive severity poorly responsive to standard therapeutic measures, regardless of disease severity or phenotypic variant. If not recognized and managed appropriately, asthmatics portends the risk of acute ventilatory failure and even death [9].

Classification of Asthma Depending on Severity [10]:

TABLE 2: CLASSIFICATION OF ASTHMA DEPENDING ON SEVERITY

Severity*		Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Features of asthma symptoms	Frequency	Less than once a week	Once or more a week, not every day	Every day	Every day
	Intensity	Mild and brief	Disturbs daily life or sleep at least once a month	Disturbs daily life or sleep at least once a week	Restricts daily life
				Worsens frequently	Worsens frequently
	Symptoms at night	Less than twice a month	Twice or more a month	Once or more a week	Frequently
PEF FEV1**	%FEV1, %PEF	≥80%	≥80%	≥ 60%, < 80%	<60%
	Diurnal variation of PEF	20%	20-30%	>30%	>30%

*Determine the severity based on the presence of any one of the features or measured percentages. FEV- Forced expiratory volume, PEF - peak expiratory flow.

Diagnosis of Asthma [11]: Asthma is diagnosed primarily when the following three conditions are true:

1. Episodic symptoms of obstruction of airflow are present.
2. Airflow obstruction is at least partially reversible.
3. History and physical examination exclude possible alternative causes of this airflow obstruction.

Symptoms of Asthma: These symptoms and signs can vary throughout the day and sometimes present only at night.

- Intermittent wheezing, chest tightness, shortness of breath, or cough, especially at night, and Symptoms vary throughout the day or the week
- Symptoms worsen at night, while exercising, or in the presence of allergens or irritants
- History of allergic rhinitis or atopic dermatitis

- Wheezing develops with specific triggering factors.
- A targeted physical exam may reveal:

Hyperion of the thorax, Expiratory wheezing, prolonged or forced exhalation, Nasal secretions, sinusitis, rhinitis, nasal polyps, Atopic dermatitis or eczema, or allergic skin problems.

The diagnosis of asthma is established primarily through a positive history and physical examination as noted above. It can be confirmed by referral for pulmonary spirometry, spirometry should be performed if possible during the time that the patient has some symptoms and is based on measurement of the Forced Expiratory Volume in the first second (FEV1) and the Forced Vital Capacity (FVC), both at rest and after the inhalation of a short-acting inhaled beta 2 agonist such as salbutamol. Confirmation of asthma is obtained with the following results:

- ✓ The FEV1is less than 80% the predicted value based on the patient's height and weight.
- ✓ The ratio of FEV1/FVC is less than 65% of the lower limit of normal for the patients age and size.
- ✓ The FEV1 increases more than 12% after inhaling a short-acting inhaled beta$_2$agonistsuch as salbutamol.

Initial Evaluation:
History: Ask specifically about the following, and try to quantify the:

Episodes of wheezing, Sensation of tightness in the chest or chest pain (especially in children), shortness of breath when resting or with mild exercise, Cough, dry or productive, Frequent colds or upper respiratory infections (URI), especially with URI that take >10days to resolve

- Symptoms that worsen at night, especially cough.
- Possible factors that may be triggering asthma episodes, such as:

Physical Examination: General examination should assess:

- ➢ Degree of dyspnea is assessed by assessment of speech which may be interrupted by the effort to breathe, cyanosis, anxiety or restlessness, use of accessory muscles for respiration.
- ➢ Respiratory and pulse rate.
- ➢ Blood pressure (elevated BP often accompanies the anxiety of respiratory distress; decreased BP can indicate severe cardiac decompensation with respiratory failure).
- ➢ Presence of pulsusparadoxicus – an INCREASE in the strength of the pulse with inspiration.
- ➢ Differentiation between inspiratory stridor and expiratory wheezing (especially in children).

Respiratory:

- Use of accessory muscles of respiration – specifically the neck and trapezius muscles.
- Degree of air movement (possible prolonged expiratory phase, or silent chest).
- Presence and location of expiratory wheezing.
- Presence and location of crackles or rales.

Diagnostic Tests and Procedures: The initial investigation should include the following:

- ✓ Measurement of peak flow as a baseline for future reference.
- ✓ Possible chest X-ray, with a focus on possible infiltrates indicating viral or bacterial pneumonia, Possible cardiomegaly or evidence of heart failure (which can cause "cardiac asthma"), Possible hyperinflation of the chest and lungs, with flattening of the diaphragm, Possible inhaled foreign body with unilateral hyperexpansion (especially in children).

In selected or severe cases, some additional investigations may be indicated:

- ❖ When possible, referral for spirometry at rest and after salbutamol inhalation, measuring both the FVC and FEV1, as noted above in the "Diagnosis of Asthma"

- Sinus X-rays if history or examination suggests chronic sinusitis.
- Oxygen saturation, or blood gas measurement.
- Chest X-ray to identify problems such as atelectasis, pneumothorax, pneumo-mediastinum, *etc*.

Other Causes of Chronic Cough and Occasional Respiratory Distress: Early pulmonary tuberculosis – This can present in the early stages with cough, intermittent wheezing and crackles, and chest pain; however, it can usually be distinguished by the steady progression and worsening of symptoms, appetite loss, weight loss, abnormal chest X-ray.

Cystic Fibrosis: A congenital disease with thickened pulmonary mucous and secondary infections – may sometimes be associated with wheezing and respiratory difficulty.

Asthma Triggers [12]: An asthma trigger is anything that irritates your airways and sets off your asthma symptoms The symptoms of asthma can be triggered by several external factors Respiratory infections such as viruses, Fungi, bacteria, and parasites, Allergens such as pollen, dust mites and animal fur or feathers, Airborne irritants like cigarette smoke, chemical fumes, and atmospheric pollution, Medicines like NSAIDS like aspirin and ibuprofen, β-blockers, Emotional factors like stress or laughing.

Anxiety, laughter, crying, and Foods containing sulphites and others like Weather conditions, such as cold air.

Morphologic Features of Asthma [4]: The pathologic changes are similar in both major types of asthma. The pathologic material examined is generally autopsy of lungs in patients dying of status asthmatics but the changes are expected to be similar in non-fatal cases.

Grossly: The lungs are over-distended due to over-inflation. The cut surface shows characteristic occlusion of the bronchi and bronchioles by viscid mucus plugs.

Microscopically: The following changes are observed:

1. The mucus plugs contain normal or degenerated respiratory epithelium forming twisted strips called *Churchman's spirals*.
2. The sputum usually contains numerous eosinophils and diamond-shaped crystals derived from eosinophils called Charcot-*Leyden crystals*.
3. The bronchial wall shows thickened basement membrane of the bronchial epithelium, submucosal oedema and inflammatory infiltrate consisting of lymphocytes and plasma cells with a prominence of
4. eosinophils. There is hypertrophy of the submucosal glands and the bronchial smooth muscle.
5. Changes of bronchitis and emphysema may ensue, especially in intrinsic asthma.

Asthma as an Inflammatory Illness [13, 14]: Asthma is associated with airway wall inflammation. Increased numbers of various types of inflammatory cells, most notably eosinophils but basophils, mast cells, macrophages and certain types of lymphocytes, can be found in airway wall biopsies and bronchoalveolar lavage fluid from asthmatic patients. Inflammatory mediators and various cytokines also are increased in the airways of asthmatic subjects compared with healthy control subjects. Even asthmatics with normal baseline lung function and no recent asthma exacerbations have increased inflammatory cells in their airways. Conversely, many individuals allergic to inhaled allergens have evidence of lower airway inflammation but suffer only from the symptoms of allergic rhinitis. Epidemiological studies show a strong correlation between increasing IgE levels and the prevalence of asthma regardless of atopic status [13].

Inhaled antigen activates mast cells and Th_2 cells in the airway. They in turn, induce the production of mediators of inflammation and cytokines, including IL-4 and IL-5. IL-5 travels to the bone marrow and causes terminal differentiation of eosinophils. Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with selectins and eventually adhering to the endothelium through the

binding of integrins to members of the immunoglobulin superfamily of adhesion proteins: VCAM-1 and ICAM-1. As the eosinophils enter the airway matrix through the influence of various chemokines and cytokines, their survival is prolonged by interleukin-4 and GM-CS. On activation, the eosinophil releases inflammatory mediators, such as leukotrienes and granule proteins, to injure airway tissues. In addition, eosinophils can generate Granulocyte–macrophage colony-stimulating factor to prolong and potentiate their survival and contribution to persistent airway inflammation [15]. The inflammatory cascade also leads to the activation of resident cells within the airways, which can produce a panoply of cytokines, growth factors, chemokines, and autacoids. The chronic inflammatory response, over time, leads to epithelial shedding and reorganization, mucous hypersecretion and airway wall remodeling, most often exemplified by sub-epithelial fibrosis and smooth muscle hyperplasia [13].

Relationship of Airway Inflammation and Lung Function [16]:

Airway Hyper-responsiveness: An important feature of asthma is an exaggerated bronchoconstriction response to various stimuli. Airway hyper-responsiveness leads to clinical symptoms of wheezing and dyspnea.

Airflow Obstruction: Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

Acute Bronchoconstriction: Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from the mast cell that includes histamine, tryptase, leukotrienes, and prostaglandins, which directly contract airway smooth muscle. In addition, other stimuli, including exercise, cold air, and irritants, can cause acute airflow obstruction. There is emerging evidence that stress can play a role in precipitating asthma exacerbations.

Airway Edema: Increased microvascular permeability and leakage caused by released mediators also contribute to the mucosal thickening and swelling of the airway. Consequently, swelling of the airway wall causes the airway to become more rigid and interferes with airflow.

Chronic Mucus Plug Formation: In severe intractable asthma, airflow limitation is often persistent. This change may partly arise due to mucus secretion and the formation of inspissated mucus plugs.

Airway Remodeling [16, 19]: Chronic inflammation in the lungs results in the development of airway remodeling involving airway wall thickening, mucus cell hyperplasia, sub-epithelial fibrosis, collagen deposition, and increased smooth muscle cell mass. The main cytokines involved in airway remodeling include TGF-h and IL-11 [17]. It is a collective term that can be defined as persistent changes to normal airway structure involving changes in the composition, organization, and function of structural cells and enhanced turnover of extracellular matrix components. Structural changes include subepithelial fibrosis, which contributes to the thickening of airway walls due to the deposition of extracellular matrix proteins such as collagens, laminin, and tenascin. Mucous gland hyperplasia leads to excessive mucus secretion and can, in severe cases, lead to occlusion of the airways. Thus, airway remodeling results in thickened airway walls in asthma. However, airway remodeling is postulated to be a determinant of AHR and the accelerated loss of lung function over time documented in many asthmatics [18]. As a result of this chronic inflammation, airway tissue is continuously being injured and healed, leading to structural changes in the airways that may account for the decline in airway function seen in patients over the years. These structural changes are collectively referred to as airway remodeling [19].

Two Key Differences between the Pathology of Asthma and Eosinophilic Bronchitis (EB): In the case of asthma, the concentration of IL-13 is elevated in the induced sputum of subjects with asthma but not subjects with EB. The numbers of IL-13 cells in the airway mucosa in asthma is relatively low but increased when compared with EB, with most of the IL-131 cells identified as eosinophils [20].

Mediators of Asthma [21]: Cells involved in inflammatory processes present in asthma produce and release numerous mediators responsible for many of the pathophysiologic changes. It has been

proposed that for a substance to be defined as a mediator, three criteria must be fulfilled;

- It must be capable of producing the pathologic changes observed in asthma or physiologic changes that define asthma.
- It must be produced in lung during an asthmatic episode and measurable in body fluids.
- Removal by specific inhibition or antagonism results in amelioration or attenuation of asthmatic response.

TABLE 3: ACTION OF MEDIATORS IN ASTHMA

Mediator	Source	Action
Major Basic Protein	Eosinophils	Epithelial damage
Histamine	Mast cells	Smooth muscle constriction, mucosal edema, mucus secretion
Leukotrienes (LTB_4 ,LTC_4 LTD_4 ,LTE_4)	Mast cells, basophils, eosinophils, neutrophil, macrophages, monocytes	Smooth muscle constriction, mucosal edema and inflammation ,
Prostaglandins PGD_2 , PGE_2 , PGF_2 , PGI_2	Mast cells, endothelial cells	Smooth muscle constriction mucosal edema, mucus secretion
Platelet Activating factor	Mast cells, basophils, eosinophils, neutrophil, macrophages, monocytes, platelets, endothelial cells.	Smooth muscle constriction, mucosal edema and inflammation, mucus secretion, Bronchial hyperresponsiveness
Thromboxanes (TXA_2)	Macrophages, monocytes, platelets.	Smooth muscle constriction, mucus secretion

ICAM– intercellular cell adhesion molecule-1, VCAM - vascular cell adhesion molecule-1.

Eosinophils [22]: Eosinophils are present in peripheral blood, bronchial mucosa, and bronchioalveolar lavage fluid of patients of asthma, and number of cells has been correlated with degree of hyperresponsiveness. Eosinophils are source of lipid-derived mediators (leukotrienes) and eosinophil granule contain majoar basic protein (MBP), eosinophil cationic factor (ECF), eosinophil-derived neurotoxin and eosinophil peroxidase. Eosinophils also generate cytokines and appear to regulate the function of eosinophils rather than having broader inflammatory effects. MBP and ECF are detectable in sputum of asthmatic patients and may be responsible for much of damage to airway epithelium, which may in turn contribute to airway hyperresponsiveness.

Eosinophil Effectors Functions: The eosinophil granule proteins are toxic to respiratory epithelium, and concentrations of these proteins in the toxic range are present in respiratory secretions from patients with asthma. The toxicity to the respiratory epithelium is manifested by epithelial cell desquamation, frank damage to epithelial cells, alterations in ciliary beating and epithelial secretion. Eosinophil granule proteins also stimulate various cells, like basophils, rat mast cells, neutrophils, respiratory goblet cells and platelets.

Potential Involvement of Eosinophils in Airway Remodeling [23]: Eosinophils produce a wide range of proteins involved in fibrogenesis and angiogenesis, as well as cytokines, which activate various mesenchymal cells and induce the synthesis of ECM proteins. Activation of fibroblasts is a property of IL-4, IL-6, IL-11, IL-13, IL-17, TGF-b, NGF, and PDGF. This, in turn, can lead to fibroblast migration and differentiation to the fibroblast phenotype, trans-differentiation of my fibroblasts to ASM cells, and the migration of various mesenchymal cells and ECM synthesis. The pericyte is also involved in these trans-differentiation processes. TGF-b transforming growth factor and FGF-2 directly affect ASM, such as proliferation and protein synthesis.

Cytokines: Cytokines are produced in response to inflammatory stimuli mainly by macrophages and Th cells but also by other inflammatory cells, vascular cells, and adiposities [15].

The Th_2-derived cytokines IL-4, IL-5, IL-9 and IL-13, and IL-3 and GM-CSF, induce many of the features of allergy and asthma. Allergen-specific T cell ‘tolerance’ or hyposensitization is a major mechanism in both allergen immunotherapy and treatment with T cell peptides.

One of the immunopathological hallmarks of atopic allergic disease, including asthma, is the infiltration of affected tissue by cells with a Thelper 2-type cytokine profile. Th2-type cytokines IL-4, IL-5, IL-9 and IL-13 influence various events associated

with chronic allergic inflammation. These include IgE production (IL-4, IL-13), maturation of eosinophils (IL-5, IL-9), upregulation of the eosinophil/ basophil-selective vascular cell adhesion molecule-1 (IL-4, IL-13), mast cell development (IL-3, IL-9), airway hyperresponsiveness (IL-5, IL-9, IL-13) and mucus overproduction (IL-4, IL-9, IL-13) [23].

Cysteinyl-leukotrienes: They are potent bronchoconstrictor derived mainly from mast cells. They are the only mediator whose inhibition has been specifically associated with improving lung function and asthma symptoms. Recent studies have also shown leukotriene B_4 can contribute to the inflammatory process by recruiting neutrophils.

Nitric Oxide (NO) [13, 24]: Is produced predominantly from the action of inducible NO synthase in airway epithelial cells; it is a potent vasodilator. Measurements of fractional exhaled NO (FeNO) may be useful for monitoring response to asthma treatment because of the purported association between FeNO and inflammation in asthma.

Under basal conditions, small amounts of NO are synthesized by constitutive NO synthase (cNOS) isozymes present in the airway epithelium [endothelial NOS and neuronal NOS (nNOS)] and in inhibitory nonadrenergic noncholinergic (iNANC) nerves (nNOS).

Activation of cNOS isozymes by either contractile agonists or depolarization (iNANC nerves) causes relaxation of the airway smooth muscle by increasing the production of cGMP and/or opening Ca2þ-activated Kþ (KCa) channels, thereby reducing airway responsiveness to contractile stimuli. Inducible NOS (iNOS) is induced in the epithelium by inflammatory cytokines and produces large amounts of NO. The resulting relaxation of airway smooth muscle is beneficial, whereas the pro-inflammatory and cytotoxic actions have detrimental effects [24].

Inflammatory Cells: Various cells are important in Inflammatory response because they produce and liberate mediators, which recruit other cells or have direct toxic effects, perpetuating this vicious cycle.

Mast Cells [25, 24]: (Acute response cells) are important in initiating inflammatory responses after exposure to allergens and the resulting immediate bronchoconstriction. After the allergen binds to IgE-bound high-affinity receptors on the surface of mast cells, various immediate-acting mediators such as histamine, leukotrienes, prostaglandins, and PAF are released, which cause immediate bronchoconstriction. In addition, several long-acting mediators are released, such as eosinophil and neutrophil chemotactic factors, TNF- α, and cytokines such as IL-4, IL-8, and IL-13, which promote an airway inflammatory response.

IgE-Dependent Release of Inflammatory Mediators [26]: IgE binds to high- and low-affinity receptors (FcεRI or FcεRII) on effector cells. The inflammatory cascade is initiated when an allergen cross-links a critical mass of IgE antibodies bound to effector cells. This results in the degranulation of effector cells and the release of a comprehensive array of mediators causally linked to the pathophysiology of allergic asthma. Immediately release of mediators includes histamine, TNF- α, proteases, and heparin over the minutes' release include lipid mediators, Prostaglandins, and leukotrienes. Over hours release includes cytokines, specifically IL- 4, and IL-13.

Role of Mast Cells in Allergy and Asthma [26]: Triggering of mast cells plays an important role in eliciting the immediate phase of an allergic response leading to acute local responses such as oedema formation, tissue swelling, or bronchoconstriction. By releasing chemotactic and pro-inflammatory mediators, mast cells can also affect the late-phase responses of an allergic response. Because of their close anatomical association with sensory nerves, bi-directional communication between mast cells and nerves can further influence inflammatory responses. The role of mast cells in the pathogenesis of asthma has been studied in diverse animal models. Especially the use of genetic mast cell-deficient mice (C57BL/6-KitW/Wv or C57BL/6-KitW-sh/W-sh) combined with mast cell reconstitution protocols (mast cell knock-in) has been very useful in delineating the role of mast cells, mast cell-expressed receptors and mast cell-derived mediators in asthma and allergy.

A mouse model for chronic asthma demonstrated that multiple exposure to antigen resulted in FcRγ-dependent (*via* IgE and/or IgG1) and FcRγ-independent mast cell activation. This mast cell activation contributed to the induction of enhanced airway responsiveness and chronic inflammation, including eosinophil and lymphocyte infiltration, goblet cell hyperplasia, and increased lung collagen levels. Other studies showed that the development of late-phase airway hyperreactivity and airway inflammation was dependent on the mast cell-induced liberation of TNF-α [26].

Products of Mast Cell Activation Include:

1. Histamine.
2. Proteases include tryptase, carboxypeptidase, chymase, Cathepsin G, elastase, plasminogen activator, rennin, matrix metalloproteinase 9.
3. Proteoglycans include heparin and chondroitin sulphate.
4. Cytokines includeIL-4,IL-5, IL-6, IL-8, IL-13, GSM-CSF,TNF – α, fibroblast growth factor, stem cell factor.
5. Lipid mediators include prostaglandin D, leukotrine C_4, PAF.
6. Other enzymes include β hexosaminidase, β-glucoronidase and aryl sulphatase.

Macrophages: Alveolar macrophages, normally present in the lumen of large and small airways, produce and release a numbers of mediators thought to be involved in the initiation and amplification of the inflammatory process. These include leukotrienes, PAF, and eosinophil and neutrophil chemotactic factors. Additionally, macrophages may be activated by IgE-dependent mechanisms. Macrophages may act as antigen presenting cells by preparing for presentation to T lymphocytes [27].

Lymphocytes [27]: T lymphocytes play an important role in the pathogenesis of asthma by coordinating the inflammatory response by producing cytokines. In contrast, B lymphocytes are involved in IgE production. The T lymphocytes include the subsets Th0.Th1.Th2; each subset secretes specific cytokines. Cytokines produced by T lymphocytes include Il-2 IL-3, Il-5, IL-6, Il-10, GM-CSF, interferon γ (INF- γ) and TNF β.

T lymphocytes in Asthma: In genetically susceptible individuals, allergen interacts with dendritic cells and CD_4^+ T cells, leading to the development of Th_0 helper lymphocytes, which give rise to a clone of helper Th_2 lymphocytes. These then generate a cytokine environment that switches β cells/plasma cells to the production and release of IgE; and also generates IL-5, which promotes differentiation and activation of eosinophils; also it is responsible for the production of IL-4 and IL-13 that induce expression of IgE receptors, mainly on mast cells but also on eosinophils. It is believed that a decrease in activation of the Th1 wing of the response allows for the allergen-induced priming of the immune response for asthma. Glucocorticoids inhibit the action of the cytokines specified [28, 27].

Basophils: After re-exposure to the antigen that binds IgE on the FcεRI receptor, basophils are recruited to the bronchial mucosa and activated, leading to granule exocytosis and mediator release [19].

Neutrophils: The activation of peripheral blood neutrophils results in their intravascular migration, adhesion to the endothelium, and migration to the site of inflammation. Nocturnal asthma is associated with high levels of neutrophils, which correlate with the severity of the disease. Neutrophils also predominate more frequently than eosinophils in the sputum of patients with acute asthma exacerbations, mostly associated with respiratory tract infection. The most significant and well-characterized chemotactic and activating factor for neutrophils is CXC chemokine ligand (CXCL)8 (IL-8), whose biological activity is mediated by two specific membrane receptors: CXC-chemokine receptor (CXCR)1 and CXCR2 [19].

Dendritic Cells (DC): Besides their important antigen-presenting role, DCs also play a role in the chemotaxis of T cells in ongoing inflammation. Interestingly, the production of CCR4 ligands (CCL17 and CCL22) by myeloid DCs suggests that these cells can recruit Th_2 cells and/or CD_4^+ CD_{25}^+ regulatory cells at sites of inflammation during the LAR.

The total number of lung DCs is increased in bronchial tissue of asthmatics, which could be an important factor in the persistence of chronic T cell-mediated allergic inflammation. Once allergen-specific Th_2 memory cells are drawn into the lung, repeated allergen presentation by lung DCs may drive the persistent stimulation of allergen-specific memory Th_2 cells. This repeated Th_2 cell stimulation would be expected to exacerbate acute asthma episodes and perpetuate chronic inflammation that contributes to the remodeling and AHR that characterize chronic asthma [19].

Role for Adenosine in Asthma [29]: Adenosine has been shown to cause bronchoconstriction in asthmatics but not in non-asthmatics. As such, adenosine could serve as a useful diagnostic test for bronchial hyperactivity. The mechanism by which adenosine causes bronchoconstriction has been suggested to involve an indirect effect on mast cells, in which ongoing mediator release is enhanced by adenosine, rather than a direct effect on the airway. That adenosine causes bronchoconstriction allied to the likelihood that concentrations of adenosine are elevated in asthma has led to an initiative in which adenosine receptors have been mooted as potential targets for therapeutic intervention. This approach has been accompanied by the development of animal models of adenosine in asthma.

Toll-like Receptors: An area of topical interest that could be of relevance in asthma is the identification of TLRs, which serve as receptors for products generated by pathogens. TLRs mediate the innate immune response to pathogens and have been identified on a wide variety of inflammatory cells. As mast cells serve an important role in innate immunity given that high numbers are found at sites where pathogens might first gain entry. Studies in cord blood-derived human mast cells have demonstrated that exposure to peptidoglycan or lipopolysaccharide, TLR_2 and TLR_4 [30].

Neural Mechanisms in Asthma: Cholinergic nerves are the predominant bronchoconstrictor pathway in airways and cholinergic neurotransmission may be increased in asthma by the effects of inflammatory mediator son afferent nerves and on prejunctional receptor son postganglionic nerves. In addition there may be a defectin prejunctional M_2-receptors on cholinergic nerves resulting in increased cholinergic neural effects. It is possible that i-NANC function may be abnormal in asthma as a consequence of inflammation [31].

Anti-Oxidantsin Asthma [32]: Reactive oxygen species released from eosinophils, alveolar macrophages, and neutrophils, seem to play a key role in asthma. They may directly contract airway smooth muscles, stimulate histamine release from mast cells and mucus secretion. Asthma is, therefore, also associated with oxidative-ant oxidative imbalance. Antioxidants such as vitamin-A/βcarotene, vitamin-C, vitamin-E and selenium are important dietary constituents that may prevent oxidative injury. Therefore, they may reduce inflammation caused by allergen exposure

CONCLUSION: This redundancy offers researchers a wide range of prospective therapeutic targets for suppressing allergy disorders. Given the complex nature of the allergic cascade and the effects of mediators at different points in the chain, not all of these prospective targets are likely to be equally promising.

IgE and IL-4 are two significant therapeutic targets that have advanced the most in human studies nowadays. Researchers are still actively looking into these two therapeutic targets as they work to create extremely effective new medicines for allergic illnesses. Also, antioxidants may play a major role in boosting the immune system.

ACKNOWLEDGEMENT: Authors thank Prof. Dr. Manohar J. Patil, Sir, Principal, Marathwada Mitramandals College of Pharmacy, Pune, for providing support.

CONFLICTS OF INTEREST: The authors declare that they have no competing interests

REFERENCES:

1. McFadden ER: Acute Severe Asthma. Am J Respir Crit Care Med 2003; 168: 740–759..
2. Djukanović R, Roche WR, Wilson JW, Beasley CRW, Twentyman OP, Howarth PH and Holgate ST: Mucosal Inflammation in Asthma. Am Rev Respir Dis 1990; 2: 434–457. https://doi.org/10.1164/ajrccm/142.2.434.
3. Carroll N, Elliot J, Morton A and James A: The Structure of Large and Small Airways in Nonfatal and Fatal Asthma. Am. Rev Respir Dis 1993; 2: 405–410. https://doi.org/10.1164/ajrccm/147.2.405

4. Harshmohan: Textbook of Pathology, Harshmohan The health sciences publishers. The Respiratory system, 7th edition 464-465.
5. Global Initiaive for Asthma, Global Strategy for Asthma management and prevention, Updated 2019.
6. Cawley MJ: Exercise-Induced Asthma. J Pharm Pract 2003; 1: 59–67.
7. Aggarwal B, Mulgirigama A and Berend N: Exercise-Induced Bronchoconstriction: Prevalence, Pathophysiology, Patient Impact, Diagnosis and Management. Npj Prim. Care Respir Med 2018; 1: 31. https://doi.org/10.1038/s41533-018-0098-2.
8. Aggarwal B, Mulgirigama A and Berend N: Exercise-Induced Bronchoconstriction: Prevalence, Pathophysiology, Patient Impact, Diagnosis and Management. Npj Prim. Care Respir Med 2018; 1: 31. https://doi.org/10.1038/s41533-018-0098-2.
9. Chakraborty RK and Basnet S: Status Asthmaticus. 2022 Oct 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 30252326.
10. Ichinose M, Sugiura H, Nagase H, Yamaguchi M, Inoue H, Sagara H, Tamaoki J, Tohda Y, Munakata M, Yamauchi K and Ohta K: Japanese Society of Allergology. Japanese guidelines for adult asthma 2017. Allergol Int. 2017; 2: 163-189. doi: 10.1016/j.alit.2016.12.005. Epub 2017 Feb 11. PMID: 28196638.
11. Primary Health Care service delivery guidelines IRAQ 2013, diagnosis and management of Asthma https://www.cdc.gov/asthma/triggers.html
12. Benjamin Burrow MD, Farnando D, Martinez MD, Merilyn Halonen, Robert AB and Martha GC: Association of Asthma with serum IgE levels and skin test reactivity to allergen, The New England J of Medicine 1989; 5: 271-77.
13. Habib N, Pasha MA, Tang DD: Current Understanding of Asthma Pathogenesis and Biomarkers. Cells 2022; 17: 2764. https://doi.org/10.3390/cells11172764.
14. National Heart and Blood Institute, National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report 2007.
15. Murdoch JR and Lloyd CM: Chronic Inflammation and Asthma. Mutat. Res. Mol. Mech. Mutagen 2010; 1: 24–39. https://doi.org/10.1016/j.mrfmmm.2009.09.005.
16. Arpita S, Bharadwaj AS, Bharadwaj, Againdra K. Bewtra AK, Bewtra and Devendra K and Agrawal DK Agrawal: Dendritic cells in allergic airway inflammation. Canadian Journal of Physiology and Pharmacology 2007; 7: 686-699. Ht tps://doi.org/10.1139/Y07-062.
17. Lloyd CM and Robinson DS: Allergen-Induced Airway Remodelling. Eur Respir J 2007; 5: 1020–1032.
18. Verstraelen S, Bloemen K, Nelissen I, Witters H, Schoeters G and Heuvel RVD: Cell Types Involved in Allergic Asthma and Their Use in *in-vitro* Models to Assess Respiratory Sensitization. Toxicol *in-vitro* 2008; 6: 1419–1431. https://doi.org/10.1016/j.tiv.2008.05.008.
19. Bradding P, Walls AF and Holgate ST: The role of the mast cell in the pathophysiology of asthma. J Allergy Clin Immunol 2006; 6: 1277-84. doi: 10.1016/j.jaci.2006.02.039. Epub 2006 Apr 27. PMID: 16750987.
20. Bradding P: The Role of the Mast Cell in Asthma: A Reassessment: Curr. Opin. Allergy Clin. Immunol 2003; 1: 45–50. https://doi.org/10.1097/00130832-200302000-00008.
21. Hall S and Agrawal DK: Key Mediators in the Immunopathogenesis of Allergic Asthma. Int. Immunopharmacol 2014; 1: 316–329. https://doi.org/10.1016/j.intimp.2014.05.034.
22. Kay AB, Phipps S and Robinson DS: A Role for Eosinophils in Airway Remodelling in Asthma. Trends Immunol 2004; 9: 477–482. https://doi.org/10.1016/j.it.2004.07.006.
23. Prado CM, Martins MA, Tibério and IF LC: Nitric Oxide in Asthma Physiopathology. ISRN Allergy 2011; 1–13. https://doi.org/10.5402/2011/832560.
24. Bradding P, Walls A and Holgate S: The Role of the Mast Cell in the Pathophysiology of Asthma. J Allergy Clin Immunol 2006; 6: 1277–1284. https://doi.org/10.1016/j.jaci.2006.02.039.
25. Nauta AJ, Engels F, Knippels LM, Garssen J, Nijkamp FP and Redegeld FA: Mechanisms of Allergy and Asthma. Eur J Pharmacol 2008; 2–3: 354–360. https://doi.org/10.1016/j.ejphar.2008.02.094.
26. Chang Y, Al-Alwan L, Risse PA, Roussel L, Rousseau, S, Halayko AJ, Martin JG, Hamid Q and Eidelman DH: TH17 Cytokines Induce Human Airway Smooth Muscle Cell Migration. J Allergy Clin Immunol 2011; 4: 1046-1053.https://doi.org/10.1016/j.jaci.2010.12.1117.
27. Rang HP and Dale MM: The Respiratory system in Pharmacology 5th edition. Churchill Livingstone Publication 2005; 342-343.
28. Rao SB: Adenosine and its role in asthma. Indian J Clin Biochem 2001; 2:140-4. doi: 10.1007/BF02864852. PMID: 23105309; PMCID: PMC3453636.
29. Barnes PJ: How Corticosteroids Control Inflammation: Quintiles Prize Lecture 2005: Corticosteroids and Inflammation. Br J Pharmacol 2006; 3: 245–254. https://doi.org/10.1038/sj.bjp.0706736.
30. Barnes PJ: Neural mechanisms in asthma. Br Med Bull 1992; 1: 149-68. doi: 10.1093/oxfordjournals.bmb.a072531. PMID: 1352167.
31. Gupta KB and Verma M: Nutrition And Asthma, Lung India 2007; 24: 105-114.

How to cite this article:
Bhong PN, Patil PJ and Ghadage PK: Pathophysiology of asthma: a review. Int J Pharm Sci & Res 2023; 14(9):4373-83. doi: 10.13040/IJPSR.0975-8232.14(9).4373-83.